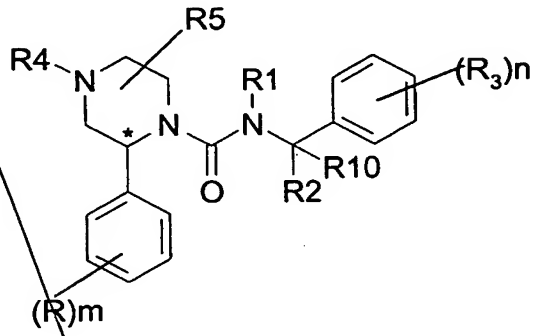
Claims

1. A compound of formula (I)



(I)

wherein

R represents a halogen atom or a C_{1-4} alkyl group;
R_1 represents hydrogen or a C_{1-4} alkyl group;
R_2 represents hydrogen, a C_{1-4} alkyl, C_{2-6} alkenyl or a C_{3-7} cycloalkyl group; or R_1 and R_2 together with nitrogen and carbon atom to which they are attached respectively represent a 5-6 membered heterocyclic group;
R_3 represents a trifluoromethyl, a C_{1-4} alkyl, a C_{1-4} alkoxy, a trifluoromethoxy or a halogen group;
R_4 represents hydrogen, a $(CH_2)qR_7$ or a $(CH_2)rCO(CH_2)pR_7$ group;
R_5 represents hydrogen, a C_{1-4} alkyl or a COR_6 group;
R_6 represents hydrogen, hydroxy, amino, methylamino, dimethylamino a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms;
R_7 represents hydrogen, hydroxy or NR_8R_9 wherein R_8 and R_9 represent independently hydrogen or C_{1-4} alkyl optionally substituted by hydroxy, or by amino;
R_{10} represents hydrogen, a C1-4 alkyl l group or
R_{10} together with R_2 represents a a C_{3-7} cycloalkyl group;
m is zero or an integer from 1 to 3; n is zero or an integer from 1 to 3; both p and r are independently zero or an integer from 1 to 4; q is an integer from 1 to 4; provided that , when R_1 and R_2 together with nitrogen and

carbon atom to which they are attached respectively represent a 5 to 6 membered heterocyclic group, i) m is 1 or 2; ii) when m is 1, R is not fluorine and iii) when m is 2, the two substituents R are not both fluorine, and pharmaceutically acceptable salts. and solvates thereof.

2. A compound as claimed in claim 1 wherein n is 2 and R_3 is trifluoromethyl both at the 3 and 5 position .

3. A compound as claimed in claim 1 or claim 2 wherein R is selected independently from halogen or a C1-4 alkyl group and m is 1 or 2.

4. A compound as claimed in any of claims 1 to 3 wherein m is 2, R is selected independently from halogen or methyl group at 2 or 4 position.

5. A compound as claimed in any of claims 1 to 4 wherein R_5 is hydrogen or a methyl group.

6. A compound as claimed in any of claims 1 to 5 wherein R_1 is hydrogen or a methyl group.

7. A compound as claimed in any of claims 1 to 6 wherein R_4 is hydrogen, a $(CH_2)rCO(CH_2)pR_7$ or $CH_2)qR_7$ group, wherein R_7 represents an amine , both p and r are independently zero or 1 ; q is 1 or 2 .

8. A compound of formula (I) as claimed in any of claims 1 to 7, wherein R is selected independently from halogen or methyl, R_3 is trifluoromethyl both at the 3 and 5 position, R_1 is hydrogen or methyl, R_2 is hydrogen, methyl, 2-propenyl or a cyclopropyl group or together with R_1 is a 3,6-dihydro-2H-pyridin-1yl, a piperidin-1-yl or a pyrrolidin 1-yl group, R_{10} represents hydrogen, a methyl or R_{10} together with R_2 is a cyclopropyl group, R_4 is hydrogen, an aminoacetyl or amino ethyl group and R_5 is hydrogen or a methyl group.

9. A compound of formula (I) as claimed in any of claims 1 to 8, wherein R is selected independently from halogen or methyl and m is 2, R_3 is trifluoromethyl both at the 3 and 5 position, R_1 and R_2 are independently hydrogen or methyl, R_4 is hydrogen and R_5 is hydrogen.

10. A compound selected from:
2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;
2-(2-Isopropyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;
2-(4-Fluoro-3-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;
2-(2,4-Difluoro-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;
2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide;
2-(4-Fluoro-phenyl)- piperazine-1-carboxylic acid (3,4-bis-trifluoromethyl-benzyl)-methyl-amide;
2-Phenyl-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl- amide;
2-(2,4-dichloro-phenyl)-piperazine-1-carboxylic acid (3,5-bistrifluoro methyl-benzyl)-methyl-amide;
2-(3,4-dichloro-phenyl)-piperazine-1-carboxylic acid (3,5-bistrifluoro methyl-benzyl)-methyl-amide;
2-(4-Fluoro-2-methyl-phenyl)-3-methyl-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;
2-(2-Methyl-4-Fluoro-phenyl)-6-Methyl- piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;
2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide;
4-(2-Amino-acetyl)-2-(S)-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide ;
2-(S)-(4-Fluoro-2-methyl-phenyl)-4-(piperidine-4-carbonyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;

4-(2-Amino-ethyl)-2-(S)-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;
2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [(1-3,5-bis-trifluoromethyl-phenyl)-cyclopropyl]-methyl-amide;
[2-(3,5-Bis-trifluoromethyl-phenyl)-pyrrolidin-1-yl]-[2-(S)-(4-fluoro-2-methyl-phenyl)-piperazin-1-yl]-methanone;
[2-(3,5-Bis-trifluoromethyl-phenyl)-3,6-dihydro-2*H*-pyridyn-1-yl]-[2-(S)-(4-fluoro-2-methyl-phenyl)-piperazin-1-yl]-methanone;
2-(3,5-Bis-trifluoromethyl-phenyl)-piperidin-1-yl]-[2-(S)-(4-fluoro-2-methyl-phenyl)-piperazin-1-yl]-methanone;
2-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)-but-3-enyl]-methyl-amide;
2-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propyl]-methyl-amide;
2-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [(3,5-bis-trifluoromethyl-phenyl)-cyclopropyl-methyl]-methyl-amide;
and enantiomers, pharmaceutically acceptable salts (e.g hydrochloride, methansulphonate, acetate) and solvates thereof.

11. 2-(S)-(4-Fluoro-2-methyl-phenyl)-4-(piperidine-4-carbonyl)-piperazine-1carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide hydrochloride.

12.4-(2-Amino-acetyl)-2-(S)-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide hydrochloride.

13.2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide ethansulphonate.

14. 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide acetate.

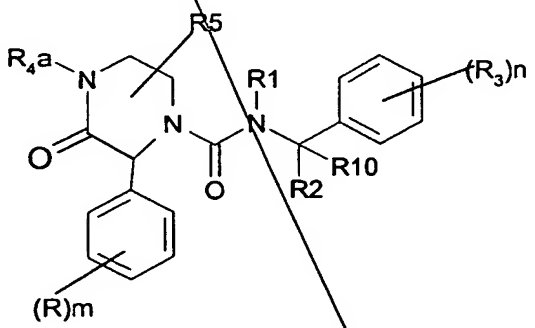
15. A compound as claimed in any of claims 1 to 14 for use in therapy.

16. The use of a compound as claimed in any of claims 1 to 14 in the preparation of a medicament for use in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins.

17. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 14 in admixture with one or more physiologically acceptable carriers or excipients.

18. A method for the treatment of a mammal, including man, in particular in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins, comprising administration of an effective amount of a compound claimed in of any claims 1 to 14.

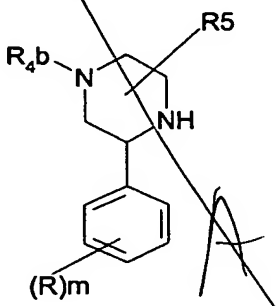
19. A process (A) for the preparation of a compound of formula (I) as claimed in claim 1, wherein R_4 is hydrogen or a $(CH_2)qR_7$ group, provided that when R_5 is a C_{1-4} alkyl or a COR_6 group, R_5 is not in the 3 position of the piperazine ring, which comprises reduction of a compound of formula (II), wherein R_{4a} is hydrogen or a suitable nitrogen protecting group or R_{4a} is a $(CH_2)qR_7$ group or protecting derivatives thereof; or



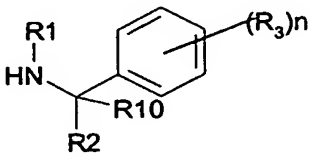
(II)

a process (B) for the preparation of a compound of formula (I) as claimed in claim 1, wherein R_4 is hydrogen or a $(CH_2)rCO(CH_2)pR_7$ group which

comprises the reaction of a compound of formula (VIII), wherein R_{4b} represents a nitrogen protecting group or R_{4b} is $(CH_2)r\ CO(CH_2)pR_7$ or a protecting group thereof with triphosgene and an organic base followed by addition of the amine (V)



(VIII)



(V)

followed where necessary or desired by one or more of the following step:

(i) removal of any protecting group;

(ii) isolation of the compound as salt thereof;

(iii) separation of a compound of formula (I) or derivative thereof into the enantiomers thereof.

Add A2

Add B12